

**REMARKS**

Claims 16-52 are pending following entry of the above amendments to the claims.

Applicant acknowledges the Examiner's statement that claims 38-52 are not rejected under section 103 over the prior art of record.

**REJECTION OF THE CLAIMS UNDER 35 U.S.C. 103**

Claims 16-37 were rejected under section 103 as obvious over WO 99/30731 taken with EP 0 619 322 or WO 98/08871.

Applicant respectfully traverses this rejection.

The Examiner has not demonstrated any reasonable expectation of success in producing needle shaped crystals in the combination of the cited references that he proposes.

Pending claims 16-37 contain two pending independent claims 16 and 26 that are directed to crystallization of a specific GLP-1 analogue [Arg<sup>34</sup>GLP-1 (7-37)] to produce needle-shaped crystals under specific conditions (100-200 mM inorganic salt, 1-15 % ethanol, 20-25 degrees Celsius, and a pH between 6 and 7).

The Examiner cites to WO99/30731 as teaching the specific conditions set forth in pending claims 16-37 as well as a method for producing an acylated GLP-1 analog which may include Arg<sup>34</sup> GLP-1 (7-37) yet states on page 5 of the Office Action that the reference does not result in the production of needle shaped crystals wherein the GLP-1 analog is Arg<sup>34</sup> GLP-1 (7-37) [indeed, the reference repeatedly states that it provides processes for preparing tetragonal flat rod shaped or plate-like crystals and the examples are all directed to the production of such crystals of Val<sup>8</sup> GLP-1 (7-37)]. Applicant submits that the Examiner's characterization of WO 99/30731 on its face renders the production of needle shaped crystals of Arg<sup>34</sup>GLP-1 (7-37) as presently claimed non-obvious and unexpected over the cited WO publication because it teaches, by the Examiner's own admission, that crystallization of GLP-1 analogs under the conditions disclosed in pending claims 16-37 does not result in the production of needle shaped crystals as presently claimed. Simply put, WO 99/30731 teaches directly away from the claimed invention.

The Examiner's citation to the secondary reference EP 0 619 322 as clearly disclosing the process of making needle shaped crystals of a GLP-1 analog is similarly flawed. In particular, the Example in the EP case to which the Examiner refers in the August 27, 2003 Office Action, Example 45, states that needle or plate shaped crystals of insulinotropin [ie GLP-1 (7-37)] were obtained "depending on the crystallization conditions" but the reference says nothing about what those conditions were. Moreover, where the EP reference does describe the preparation of microcrystalline forms of GLP-1, it discloses mixing solutions of GLP-1 (7-37) in pH 7-8.5 buffer with certain combinations of salts and low molecular weight polyethylene glycols (see Examples 35-36). These are clearly not the conditions recited in pending claims 16-37.

Moreover, even assuming *arguendo* that Example 45 somehow taught the production of needle shaped crystals of GLP-1 (7-37), the Examiner has not provided any evidence for why one would reasonably expect to obtain such crystals with Arg<sup>34</sup> GLP-1 (7-37) under the conditions recited in the pending claims, especially where crystallization of GLP-1 analogs under such conditions (as alleged by the Examiner for WO 99/30731) results in the production of crystals which are tetragonal flat rod shaped or plate-like and not needle shaped as presently claimed.

Finally, Applicant submits that one would not have been motivated by the cited prior art to select the specific analog recited in the pending claims for inclusion in the method of WO 99/30731. In particular, Applicant notes that the primary reference (WO 99/30731), and the secondary reference (WO 98/08871) which the Examiner cites to as disclosing a method for producing GLP-1 analogs including Arg<sup>34</sup>GLP-1 (7-37), disclose thousands of GLP-1 analogs and derivatives (see, for example pages 17-30 of WO 98/08871 cited to by the Examiner) and the Examiner has provided no reason, other than the impermissible use of hindsight afforded by the present disclosure, why one skilled in the art would select the single GLP-1 analog recited in pending claims 16-37 out of the thousands of analogs disclosed in the cited art.

Accordingly, in view of the above arguments, Applicant respectfully submits that pending claims 16-37 are non-obvious over the cited prior art and therefore requests withdrawal of this section 103 rejection.

**REJECTION OF THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH**

Claims 38-52 are rejected as failing to comply with the written description requirement because the pages of the specification cited by Applicant as supporting added claims 38-52 are alleged to refer to manipulations of GLP-1 analogs and not exendin-4.

In response, Applicant notes that while the cited pages (page 2, line 28, page 3, lines 16-17, page 13, lines 2-31 and page 14, lines 4-5) refer to GLP-1 analogs and solutions containing such analogs, the specification, on page 18, lines 15-25, defines "GLP-1 analogue" as including exendins (see line 25). Thus, the pages cited by Applicant in support of added claims 38-52 do provide written description for the claimed method of producing crystals of exendin. Withdrawal of this rejection is therefore respectfully requested.

**REJECTION OF THE CLAIMS UNDER 35 U.S.C. 112, SECOND PARAGRAPH**


The rejection of claims 16-25 is rendered moot by the amendment of claim 16 to recite the percentage of ethanol in (vol/vol) rather than in (w/w).

The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Please charge any deficiencies or overpayment to Deposit Account No. 14-1447.

Respectfully submitted,

Date: August 11, 2004

  
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